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ROSS J. OEHLER
AVENTIS PHARMACEUTICALS INC.
1041 ROUTE 202-206
MAIL CODE: D303A
BRIDGEWATER, NJ 08807

EXAMINER	
BERCH, MARK L	

ART UNIT	PAPER NUMBER
1624	

DATE MAILED: 03/30/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/677,683	BORCHERDING ET AL	
	Examiner	Art Unit	
	Mark L. Berch	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 February 2006* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-19,21-35 and 45-49* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3-19,21-35 and 45-49* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☒ Certified copies of the priority documents have been received in Application No. *09/998,976* .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *3/2/2006* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 3-19, 21-35, 45-49 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

1. The scope of claim 22 is not clear. What exactly qualifies as a CDK is not always agreed upon. Does it have to have the form of "CDK" followed by a numeral? Even there, the names can change over time. Thus, what once called Tau PK II is now called CDK6. What was until recently called PISSLRE is now (sometimes) called CDK10. What about the "CDK-like" kinases, which have CDK at the start, but not a numeral next, e.g. CDKL1 (also called KKIALRE) and CDKL2 (also called P56 or KKIAMRE)? Further, what about the "PCTAIRE" group (PCTAIRE1, PCTAIRE2, PCTAIRE3)? What about STK9 (serine/threonine kinase 9)? These have been (sometimes) classified with the CDKs, but do not have CDK as part of their name? Is ICK (Intestinal cell kinase) a CDK or a MAP kinase? Does it includes non-mammalian CDKs such as PHO85, SSN3 and KIN28 ? The traverse is unpersuasive. Applicants have not addressed the actual

questions raised. For example, the examiner asked "What about the "CDK-like" kinases" but there is no actual answer, yes or no. Simply saying that "a plurality of CDKs exists" does no address the question of whether non-mammalian kinases are included.

2. Claim 23's new wording is unclear. Does this mean that one is inhibiting the complex itself? It would seem that such is the intent of the wording, but claim 22 does not provide for this, only for inhibition of the CDK itself.
3. Also, the last choice has "cyclin D" but in fact, there is no such thing. There are cyclins D1, D2 and D3. The traverse is unpersuasive. As these three do find descriptive support, applicants can fix this accordingly.
4. The "substituted by a nitrogen atom" of third line below the page 5 structures is not correct. A N atom requires three bonds; no carbon in any of these rings has more than one H to displace. Did applicants mean "nitro"? Amino? Replaced by a N? For whichever choice is made, applicants must show that one of ordinary skill in the art would have known that this choice, and not another, was intended. The traverse is unpersuasive. Applicants state, "A nitrogen atom can easily replace these carbon atoms. That is the carbon can be substituted by a nitrogen atom." These are different statements. If a carbon atom is "substituted" by (or with, or at) something, that means that instead if a H atom attached to the C, there is attach the substituent. Such claim language can be seen in the following text, which has "each carbon of the aromatic ring may be independently substituted with an X substituent." If applicants intend that the Carbon be actually replaced, then they must change the wording, and show that one of ordinary skill in the art could have determined that such is what was really meant.

5. The choice of X as =O is not possible for the same reason: No carbon has two hydrogens to be replaced. Moreover, X is depicted clearly as monovalent in the structures where it appears on the top of page 5. The traverse is unpersuasive. How molecules remain in solution is irrelevant. The Oxo substituent requires two hydrogens to replace, and no carbon in these rings has two carbons.
6. The "saturated or unsaturated" for alkylene is not correct. An alkyl by its very nature cannot be unsaturated. Alkyl is a group of the formula $-C_nH_{2n+1}$, as such it cannot be unsaturated. The traverse is unpersuasive. The fix just makes matters worse. Alkylene is simply the divalent form of alkyl. Thus methylene is $-(CH_2)-$; it is not an unsaturated group. The further problem is that applicants have replaced the original monovalent groups (e.g. X) with the divalent alkylene, which leaves a dangling valence, except in cases where the term is used as a linker.
7. "Heterocyclic" (e.g. in the NR5 definition) is indefinite. What is the number and nature of the heteroatoms? Can the ring be fused or spiroconnected to another ring, and if so, what kind of ring? Can the ring be bridged? Unsaturated? Cf. *In re Wiggins*, 179 USPQ 421, 423. The traverse is unpersuasive. It does not address the problem, which is that the rest of the ring is undefined. It is of course understood that the N-of-attachment is present, but what else is in the ring?
8. The purpose of claim 47 is unclear. These are the only three choices. The claim thus does not appear to further narrow the claim that it depends on, and hence is improperly dependent on claim 23.
9. The term "mixed type of neoplasm" is unclear. Is this the same thing as "mixed neoplasm", or is it something broader? The traverse is unpersuasive. Applicants simply

say that the term "is clearly understood by the skilled artisan", but such an unsupported assertion does not answer the above questions. Applicants suggest that "An alternative ... might be "mixed cellularity neoplasia" that is used..." First, applicants have not amended the claims to use such language. Second, that is not a term of art either. The examiner ran this term in the "Google Scholar" and the Medline search engines and got zero hits.

10. Moreover, even if the term is intended to mean "mixed neoplasm", that term has no fixed meaning either. It is often used in the sense of neoplasm derived from both epithelial or mesenchymal tissues, sometimes in the sense of a tumor from more than one of the major types, such as carcinosarcoma, and sometimes any tumor which appears to have two different types of neoplasms present, regardless of their actual nature. The traverse is unpersuasive. Applicants have simply not addressed the issue at all. That is, even if "mixed type of neoplasm" really means "mixed neoplasm", that term itself is used in different ways; it does not have one generally accepted meaning. Applicants refer to "Mixed cellularity Hodgkin's lymphoma" That is the name of a particular subtype of HL, and the "Mixed cellularity" term is not used as the part of the name of any other cancer subtype so far as the examiner is aware.

11. In addition, claim 11 is unclear. This seems to be saying that e.g. Hodgkin's disease is a mixed neoplasm, which it is not. There is a type called "Mixed cellularity Hodgkin's lymphoma", but that isn't really a mixed neoplasm in the ordinary sense. Thus, the meaning of claim 11 is unclear. The traverse is unpersuasive. Applicants have not addressed the issue here at all. It is not clear, for example whther applicants agree or

disagree with the examiner's statement that Hodgkin's disease itself is a not mixed neoplasm.

12. The claim 1 "where phenyl is...." Remains unclear. Which phenyl is this? Is it any phenyl ring? Or only a phenyl which is said to be optionally substituted? Does it include the fused phenyl rings seen in the definition for W? Applicants need to note that while the claim says "where phenyl is substituted with....", earlier text has "substituted or unsubstituted phenyl". Thus, the "substituted or unsubstituted phenyl" wording makes the substitution optional, but the "where phenyl is substituted with...." wording makes it required.

Claim 12 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This claim language, which would cover e.g. viral infections, osteoarthritis, Alzheimer's Disease, etc. is beyond what the specification teaches.

Claims 3-22, 24-26, 45, 46, and 49 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Pursuant to *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988), one considers the following factors to determine whether undue experimentation is required: (A) The breadth of the claims; (B) The nature of the invention; (C) The state of the

prior art; (D) The level of one of ordinary skill; (E) The level of predictability in the art; (F) The amount of direction provided by the inventor; (G) The existence of working examples; and (H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure. Some experimentation is not fatal; the issue is whether the amount of experimentation is "undue"; see *In re Vaeck*, 20 USPQ2d 1438, 1444.

The analysis is as follows:

(1) Breadth of claims.

(a) Scope of the compounds. Doe to the deeply nested nature of the Ra variable (Ra can be NR1R3, where R1 can be a choice with Q and two W groups, and Q can have another R3 substituent, and W can be assorted rings with B (which has the R6 substituent) and several X substituents, which X substituents can have R4 and R5 substituents on them, variables which have very broad definitions), the claim covers millions if not billions of compounds. The traverse on this point is not persuasive. Applicants state, "Breadth of a claim is not sufficient grounds for rejection." The examiner has not said that it is. It is one of the factors to be considered in enablement as set forth in *In re Wands*.

(b) Scope of the diseases covered. The coverage is colossal. The following is by no means exhaustive:

A. CNS cancers cover a very diverse range of cancers in many categories and subcategories. There are an immense range of neuroepithelial tumors. Gliomas, the most common subtype of primary brain tumors, most of which are aggressive, highly invasive, and neurologically destructive tumors are considered to be among the deadliest of human cancers. These are any cancers which show evidence (histological, immunohistochemical, ultrastructural) of glial differentiation These fall mostly into five categories. There are the astrocytic tumors

(Astrocytomas): Pilocytic astrocytoma (including juvenile pilocytic astrocytoma, JPA, and pediatric Optic Nerve Glioma) Diffuse astrocytomas (including Fibrillary astrocytomas, Protoplasmic astrocytomas and Gemistocytic astrocytomas), Anaplastic astrocytomas (including adult Optic Nerve Glioma), Glioblastoma multiforme (GBM), gliosarcoma and giant cell glioblastoma, and Pleomorphic xanthoastrocytoma. GBM exists in two forms, primary and secondary, which have very different clinical histories and different genetics, but iGBM s considered to be one clinical entity. Second, there are the oligodendroglial tumors (Oligodendrogliomas): Low grade Oligodendroglioma and Anaplastic Oligodendroglioma. Third, there is oligoastrocytomas ("mixed glioma"), a type of tumor with both astrocytoma & oligodendroglioma features. The fourth type is the Ependymomas, which are intracranial gliomas, including Papillary Ependymoma, Myxopapillary ependymoma, tanycytic ependymoma, Anaplastic ependymoma and subependymal giant-cell astrocytomas. A fifth type is the Gangliogliomas (glioneuronal tumors or glioneurocytic tumors), which have both glial and neuronal components, and are extremely varied, based in part on what types of glial and what types of neuronal components are present. These include Papillary Glioneuronal Tumor (PGNT), a range of Supratentorial gangliogliomas, assorted intramedullary spinal cord gangliogliomas, Pineal ganglioglioma, Hypothalamic ganglioglioma, cerebellar ganglioglioma, Ganglioglioma of the right optic tract, rosetted glioneuronal tumor ("glioneurocytic tumor with neuropil rosettes"), composite pleomorphic xanthoastrocytoma (PXA)-ganglioglioma, desmoplastic ganglioglioma (both infantile (DIG) and non- infantile), Angioganglioglioma, and others. There are also some Glial tumors which do not comfortably fit into these five categories, notably Astroblastoma, Gliomatosis cerebri, and chordoid glioma, which is found solely in the Hypothalamus and Anterior

Third Ventricle. Other neuroepithelial tumors include astrocytic tumors (e.g. astrocytomas) oligodendroglial tumors, Ependymal cell tumors (e.g. myxopapillary ependymoma), mixed gliomas (e.g. mixed oligoastrocytoma and ependymo-astrocytomas) tumors of the choroid plexus(Choroid plexus papilloma, Choroid plexus carcinoma), assorted neuronal and Neuroblastic tumors (e.g. gangliocytoma, central neurocytoma, dysembryoplastic neuroepithelial tumor, esthesioneuroblastoma, Olfactory neuroblastoma, Olfactory neuroepithelioma, and Neuroblastomas of the adrenal gland), pineal parenchyma tumors (e.g. pineocytoma, pineoblastoma, and Pineal parenchymal tumor of intermediate differentiation), embryonal tumors (e.g. medulloepithelioma, neuroblastoma, retinoblastoma, ependymoblastoma, Atypical teratoid/rhabdoid tumor, Desmoplastic medulloblastoma, Large cell medulloblastoma, Medullomyoblastoma, and Melanotic medulloblastoma) and others such as polar spongioblastoma and Gliomatosis cerebri. A second Division is tumors of the meninges. This includes tumors of the meningothelial cells, including Meningiomas (Meningothelial, Fibrous (fibroblastic), Transitional (mixed), Psammomatous, Angiomatous, Microcystic, Secretory, Lymphoplasmacyte-rich, Metaplastic, Clear cell, Chordoid, Atypical, Papillary, Rhabdoid, Anaplastic meningioma) and the non- Meningioma tumors of the meningothelial cells (Malignant fibrous histiocytoma, Leiomyoma, Leiomyosarcoma, Rhabdomyoma, Rhabdomyosarcoma, Chondroma, Chondrosarcoma, Osteoma, Osteosarcoma, Osteochondroma, Haemangioma, Epithelioid haemangioendothelioma, Haemangiopericytoma, Angiosarcoma, Kaposi sarcoma). There are also Mesenchymal, non-meningothelial tumors (Lipomas, Angiolipoma, Hibernoma Liposarcoma, (intracranial)Solitary fibrous tumor, and Fibrosarcoma) as well as Primary melanocytic lesions (Diffuse melanocytosis, Melanocytoma, Malignant

melanoma, and Meningeal melanomatosis). A third Division are the tumors of Cranial and Spinal Nerves. This includes schwannomas (Cellular, Plexiform and Melanotic), neurofibroma, Perineurioma (Intraneural and Soft tissue) and malignant peripheral nerve sheath tumor (MPNST), including Epithelioid, MPNST with divergent mesenchymal differentiation, MPNST with epithelial differentiation, Melanotic, and Melanotic psammomatous). A fourth division are Germ Cell Tumors, including germinoma, embryonal carcinoma, yolk sac tumor, choriocarcinoma, and teratoma (Mature teratoma, Immature teratoma, and Teratoma with malignant transformation). A fifth division are the tumors of the Sellar Region, viz. pituitary adenoma, pituitary carcinoma, granular cell myoblastoma and craniopharyngiomas (Adamantinomatous and Papillary). Yet another division are local extensions from regional tumors, including paraganglioma, chodroma, chordoma, and chondrosarcoma. There are also Primitive Neuroectodermal Tumors (PNETs) including Medulloblastomas, medulloepitheliomas, ependymoblastomas and polar spongioblastomas. There are Vascular brain Tumors e.g. the hemangioblastomas, there is CNS Lymphoma (which can be primary or secondary) and Meningeal Carcinomatosis. There are Lymphoma AND Haemopoietic neoplasms including Malignant lymphomas (which can be primary or secondary), Plasmacytoma, and Granulocytic sarcoma. And there are many, many others.

B. Leukemia, named specifically in claim 5, is any malignant neoplasm of the blood-forming tissues. Leukemia can arise from many different sources. These includes viruses such as EBV, which causes Burkitt's lymphoma, and HTLV-1, linked to certain T cell leukemias. Others are linked to genetic disorders, such as Fanconi's anemia, which is a familial disorder, and Down's Syndrome. Other leukemias are caused by exposure to carcinogens

such as benzene, and some are actually caused by treatment with other neoplastic agents. Still other leukemias arise from ionizing radiation, and many are idiopathic. Leukemias also differ greatly in the morphology, degree of differentiation, body location (e.g. bone marrow, lymphoid organs, etc.) There are dozens of leukemias. There are B-Cell Neoplasms such as B-cell prolymphocytic leukemia and Hairy cell leukemia (HCL, a chronic leukemia). There are T-Cell Neoplasms such as T-cell prolymphocytic leukemia, aggressive NK cell leukemia, and T-cell granular Lymphocytic leukemia. There are different kinds of acute myeloid leukemias, acute promyelocytic leukemias, acute myelomonocytic leukemia, chronic myelomonocytic leukemia, acute monocytic leukemias, and erythroleukemias. There is also acute megakaryoblastic leukemia, acute promyelocytic leukemia, Multiple Myeloma, lymphoblastic leukemia, hypocellular acute myeloid leukemia, Ph-/BCR- myeloid leukemia, acute basophilic leukemia, and acute myleofibrosis. Chromic leukemias include chronic lymphocytic leukemia(CLL, which exists in a B-cell and a T-cell type), prolymphocytic leukemia(PLL), large granular lymphocytic leukemia (LGLL, which goes under several other names as well), chronic myelogenous leukemia(CML), chronic myelomonocytic leukemia, chronic granulocytic leukemia, chronic neutrophilic leukemia, chronic eosinophilic leukemia and many others.

C. Carcinomas of the Liver include Hepatocellular carcinoma, Combined hepatocellular cholangiocarcinoma, Cholangiocarcinoma (intrahepatic), Bile duct cystadenocarcinoma and Undifferentiated carcinoma of the liver. There are also two types of liver hemangioma: cavernous and hemangioendothelioma.

D. The main types of lung and pleural cancer are small cell (i.e. oat cell, including combined oat cell), adenocarcinoma (Bronchioloalveolar carcinomas (Nonmucinous, Mucinous, and

Mixed mucinous and nonmucinous or indeterminate cell type), Acinar, Papillary carcinoma, Solid adenocarcinoma with mucin, Adenocarcinoma with mixed subtypes, Well-differentiated fetal adenocarcinoma, Mucinous (colloid) adenocarcinoma, (these all fall within the lung adenocarcinoma of claim 8) Mucinous cystadenocarcinoma, Signet ring adenocarcinoma, and Clear cell adenocarcinoma), squamous cell (Papillary, Clear cell, Small cell and Basaloid), mesothelioma (including epithelioid, sarcomatoid, desmoplastic and biphasic) and Large Cell Carcinoma (which include Large-cell neuroendocrine carcinoma, Combined large-cell neuroendocrine carcinoma, Basaloid carcinoma, Clear cell carcinoma Lymphoepithelioma-like carcinoma, and Large-cell carcinoma with rhabdoid phenotype) (these carcinomas fall within the lung carcinoma of claim 7). In addition there are also the carcinomas with pleomorphic, sarcomatoid or sarcomatous elements, including Carcinomas with spindle and/or giant cells, Spindle cell carcinoma, Carcinosarcoma and Pulmonary blastoma. The non-small cell lung carcinomas also include Adenosquamous carcinoma, the Carcinoid tumor (both typical Carcinoid and atypical Carcinoid) as well as carcinomas of salivary-gland type, including mucoepidermoid carcinoma and adenoid cystic carcinoma. There are some soft tissue tumors including localized fibrous tumor (formerly called benign fibrous mesothelioma); epithelioid haemangioendothelioma; pleuropulmonary blastoma; chondroma; calcifying fibrous pseudotumor of the visceral pleura); congenital peribronchial myofibroblastic tumors, diffuse pulmonary lymphangiomyomatosis and desmoplastic round cell tumor. There are assorted bronchial adenomas (eg, adenoid cystic carcinomas, mucoepidermoid carcinomas, mucous gland adenomas, and oncocytomatous bronchial mucous gland adenoma) as well as other adenomas, including papillary adenoma. There are some papillomas, including squamous cell papilloma and glandular papilloma.

There is also malignant melanoma of the lung, Hamartoma, some germ cell tumors, thymoma and sclerosing haemangioma and many others as well.

E. Thyroid cancer comes in four forms: papillary thyroid cancer, follicular thyroid cancer, anaplastic thyroid cancer, and medullary thyroid cancer.

F. Carcinomas of the skin are the Basal cell carcinomas (BCC), including Superficial BCC, Nodular BCC (solid, adenoid cystic), Infiltrating BCC, Sclerosing BCC (desmoplastic, morpheic) , Fibroepithelial BCC, BCC with adnexal differentiation, Follicular BCC, Eccrine BCC, Basosquamous carcinoma, Keratotic BCC, Pigmented BCC, BCC in basal cell nevus syndrome, Micronodular BCC. Another important family is the Squamous cell carcinomas (SCC) which include Spindle cell (sarcomatoid) SCC, Acantholytic SCC, Verrucous SCC, SCC with horn formation, and Lymphoepithelial SCC, along with less well classified SCCs such as Papillary SCC, Clear cell SCC, Small cell SCC, Posttraumatic (e.g., Marjolin ulcer) and Metaplastic (carcinosarcomatous) SCC. Another family is the Eccrine carcinomas including Sclerosing sweat duct carcinoma (syringomatous carcinoma, microcystic adnexal carcinoma), Malignant mixed tumor of the skin (malignant chondroid syringoma), Porocarcinoma, Malignant nodular hidradenoma, Malignant eccrine spiradenoma, Mucinous eccrine carcinoma, Adenoid cystic eccrine carcinoma, and Aggressive digital papillary adenoma/adenocarcinoma. Other carcinomas of the skin include Epidermal carcinomas, Paget disease, Mammary Paget disease, Extramammary Paget disease Adnexal carcinomas, Apocrine carcinoma, Sebaceous carcinoma, Tricholemmocarcinoma and Malignant pilomatricoma (matrical carcinoma).

G. There are many types of colon cancers, and this category is rather diverse. Most are adenocarcinomas, either of the mucinous (colloid) type or the signet ring type (these are

named in claim 8). Less common colon cancers include squamous cell, neuroendocrine carcinomas, carcinomas of the scirrhous type, lymphomas, melanomas, sarcomas (including fibrosarcomas and Leiomyosarcomas), and Carcinoid tumors.

H. Renal carcinomas include papillary renal cell carcinoma, conventional-type (clear cell) renal carcinoma, chromophobe renal carcinoma and collecting duct carcinoma.

I. Carcinomas of the prostate, named in claim 7 and 8, are usually adenocarcinomas, but others include small cell carcinoma, mucinous carcinoma, prostatic ductal carcinoma, squamous cell carcinoma of the prostate, basal cell carcinoma, signet-ring cell carcinomas and others.

J. Penile carcinoma is usually a squamous cell carcinoma, but there is also Penile clear cell carcinoma and Sarcomatoid carcinoma.

K. The carcinomas of the extrahepatic bile ducts are of numerous types, including carcinoma in situ, Adenocarcinoma, Papillary adenocarcinoma, Adenocarcinoma (intestinal-type), Mucinous adenocarcinoma, Clear cell adenocarcinoma, Signet ring cell carcinoma, Adenosquamous carcinoma, Squamous cell carcinoma, Small cell carcinoma (oat cell carcinoma) and undifferentiated carcinoma of the extrahepatic bile ducts.

L. Sarcomas are listed in claim 9, and in mixed form in claim 11. Sarcomas are cancers in which the cancer cells arise from or resemble normal "connective tissues" cells in the body. These tumors occur at nearly all sites within the body including the head and neck, torso, retroperitoneum, pelvis, and limbs, and are quite varied. Categories and types include Liposarcomas, Leiomyosarcomas (including uterine sarcomas)which can arise nearly anywhere in the body, Rhabdomyosarcomas (of which there are many kinds, e.g. paratesticular rhabdomyosarcoma, and Pleomorphic rhabdomyosarcoma (PRMS)), Synovial

Sarcomas, which can also arise in almost any location in the body, Angiosarcomas (e.g. Liver angiosarcoma), Liposarcoma (including intra-muscular lipoma, angiolipoma and spindle cell sarcoma), Fibrosarcomas (including Fibroma), Malignant Peripheral Nerve Sheath Tumor (MPNST, also called neurofibrosarcoma), Gastrointestinal Stromal Tumor (GIST) also known as GI Stromal Sarcoma, Desmoid Tumor (Musculoaponeurotic fibromatosis), Ewing's Family of Sarcomas (e.g. Ewing's tumor of bone; extraosseus Ewing's (tumor growing outside of the bone); primitive neuroectodermal tumor (PNET); also known as peripheral neuroepithelioma; and Askin's tumor), Osteosarcoma (also known as osteogenic sarcoma e.g. Malignant fibrous histiocytoma), Chondrosarcomas (including Chondroma), Langerhans cell sarcoma, prostate sarcoma, Histiocytic sarcoma, Cystosarcoma, Osteoma, Kaposi's sarcoma, Reticulum cell sarcoma, Neurofibroma, Hemangioma, Haemangioendothelial sarcoma and Hemangiosarcoma, Neurosarcoma, Epithelioid Sarcoma, Clear Cell Sarcoma of Kidney, Myeloid sarcoma, malignant fibrous histiocytoma (MFH), Benign and Malignant Schwannoma, Lymphangiosarcoma, Neurilemmoma, Interdigitating dendritic cell sarcoma, Leydig cell sarcoma (LTW), and many others. These tumors, which can occur in soft tissue or in bones or in blood, are so diverse that it is contrary to medical understanding for them to be treated generally by any one agent, and in fact, no such agent exists. Indeed, sarcomas generally speaking do not respond particularly well to primary chemotherapy, especially as compared to many other types of tumors. Instead, sarcomas are more frequently treated with surgery, or radiation, or even regional hyperthermia (RHT), and Photodynamic therapy (PDT).

M. Melanoma, covered by claim 10, is a general type of cancer, arising primarily from cells which produce melanin, and again is distributed fairly widely in the body, including the

regional lymph nodes, skin, liver, lungs, eye, brain, and mucous membranes of the genitalia, anus, oral cavity, colon and other sites. There are a great variety of these.

N. A hyperproliferative disorder, listed in e.g. in claims 3 and 12 , beyond just cancers themselves, is anything that causes any abnormal tissue growth. That can be growth by cellular proliferation more rapidly than normal, or continued growth after the stimulus that initiated the new growth has ceased, or lack (partial or complete) of structural organization and/or coordination with surrounding tissue, all of which arise from lack of proper control of cell growth. It can be benign or malignant. Thus, such a term covers not only all cancers, but also covers precancerous conditions such as lumps, lesions, and polyps. In addition, it embraces various non-cancerous proliferative disorders such as certain types of restenosis, vascular smooth muscle proliferation associated with atherosclerosis, glomerular nephritis, pulmonary fibrosis, clonal proliferative disorders including the various Myelodysplastic Syndromes (the assorted Refractory Anemias, Ph-Chromosome-Negative Chronic Myelocytic Leukemia, Chronic Myelomonocytic Leukemia and Agnogenic Myeloid Metaplasia) and the Myeloproliferative Disorders (Chronic myelogenous leukaemia, which exists in adult and juvenile forms; Polycythemia vera;. Agnogenic myeloid metaplasia and Essential thrombocythemia). It includes certain types of abnormal wound healings. It covers numerous types of abnormal angiogenisis e.g. in certain eye diseases (such as neovascular glaucoma, diabetic retinopathy, retinopathy of prematurity, retrolental fibroplasias, and age-related and certain other types of macular degeneration), Rosacea, some neurodegenerations, respiratory distress in the premature infant, some problems in embryonic development, and atherosclerosis. It includes the myeloproliferative disorders (such as primary polycythemia, primary (essential)

thrombocythemia, chronic myelogenous leukemia and myleofibrosis). Also included are numerous Plasma cell dyscrasias, such as Multiple myeloma, Smouldering Myeloma, monoclonal gammopathy of unknown significance (MGUS), solitary plasmacytoma of bone (SPB), asymptomatic myeloma, Waldenström's macroglobulinemia, Solitary extramedullary plasmacytoma, Primary Amyloidosis, POEMS syndrome, and the three heavy-chain diseases). It also includes an assortment of skin disorders, such as psoriasis, atopic dermatitis, allergic contact dermatitis, epidermolytic hyperkeratosis, palmoplantar Pustulosis, lichenified eczema, seborrhoeic dermatitis and the keratinization disorders (including assorted ichthyoses, keratosis pilaris, keratosis follicularis, tylosis, "knuckle pads", corns, assorted callosities, and numerous keratinization disorders found in dogs and cats). Also included are LAM (Lymphangioleiomyomatosis, a smooth muscle proliferative disorder of the lungs) rheumatoid arthritis and even Alzheimer's Disease. It covers most inflammatory and immune disorders. Indeed, almost anything that the body grows --- skin, blood cells, nerves, plasma, muscles, the vascular network, can grow too fast, or in a O. The treatment of "autoimmune diseases" (claim 13) generally would be an unprecedented feat. For a compound or genus to be effective against "autoimmune diseases" generally is contrary to medical science. The "autoimmune diseases" are processes which can take place in virtually any part of the body. There is a vast range of forms that it can take, causes for the problem, and biochemical pathways that mediate the inflammatory reaction. There are dozens of such diseases, which have fundamentally different mechanisms and different underlying causes. Known autoimmune disorders include multiple sclerosis, autoimmune uveitis, rheumatoid arthritis, Addison's disease, thyroiditis, atrophic gastritis, myasthenia gravis, idiopathic thrombocytopenic purpura,

hemolytic anemia, systemic lupus erythematosus, primary biliary cirrhosis, Wegener's granulomatosis, polyarteritisnodosa, erythema nodosum leprosum, Guillain-Barré syndrome (GBS), allergic encephalomyelitis, acute necrotizing hemorrhagic encephalopathy, idiopathic bilateral progressive sensorineural hearing loss (IPBSNHL), aplastic anemia, pure red cell anemia, polychondritis, scleroderma, Stevens-Johnson syndrome, idiopathic sprue, lichen planus, Crohn's disease, Graves ophthalmopathy, sarcoidosis, primary biliary cirrhosis, type I diabetes, autoimmune optic neuritis, uveitis posterior, or interstitial lung fibrosis, alopecia, Sjogren's Syndrome, Goodpasture Syndrome, inflammatory bowel disease, Essential Mixed Cryoglobulinemia, Behcet's Syndrome, Chronic Inflammatory Polyneuritis (CIPD), CREST Syndrome, Antiphospholipid Syndrome, Relapsing Polychondritis (systemic chondromalacia or von Meyenburg disease), Retroperitoneal Fibrosis, immune dysregulation, polyendocrinopathy, enteropathy, X-linked syndrome (IPEX), and many more.

P. Claims 15-20 are drawn to prevention of apoptosis, programmed cell death, arising from different causes. Apoptosis arises from a wide variety of mechanisms, some of them very poorly understood. Apoptosis is a normal and routine body process, without with the body would soon die.

Q. Claim 21 is drawn to protecting neuronal cells from antineoplastic agents. This is an odd utility, since these compounds are themselves asserted to be antineoplastic agents. Thus these compounds are asserted to protect nerve cells (of which there are many different types) from these very compounds, which makes no sense at all. The traverse on this issue is unpersuasive. Applicants assert, without evidence that "One of ordinary skill in the art ...would have no difficulty understanding in which situations to beneficially apply the

present invention." How will this be done? Applicants have simply not addressed the central paradox that these compounds are supposed to protects cells from, in essence, themselves. Just assaying that the compounds "arrest mitotic cell division" doesn't address the point.

R. Claim 22-23 and 45-48 are drawn to inhibiting the effect of CDKs. Again, this is an essential body process; cells cannot be replaced without the activity of CDK and CDK complexes to regulate and thus assure the formation of new healthy cells. Depending of what definition of CDK is used, there could be as many as several dozen of these covered by the claim. The traverse focuses on the need for a proper "balancing act", since CDKs are absolutely essential for life. But the claims do not call for for any kind of balance. They simply inhibit all CDKs, even those that are already dangerously suppressed for some reason.

S. Restenosis, or recurrent stenosis, listed in claim 13, is an extremely general term. Stenosis is the narrowing of any canal, orifice, valve, duct, tube (such as trachea), opening, etc. in the body. These can arise from obstructive lesions, deposits of granulations, organ hypertrophy, etc. There is no such thing as being able to treat such widely diverse problems which arise from different and unrelated sources. The traverse focuses on the "renarrowing of a coronary artery after angioplasty or stenting". The claim is not so limited. Narrowing can occur from deposits (of any sort) and do not necessarily have anything to do with uncontrolled cell growth, or angiogenesis. Of course, applicants have not shown that their compounds can control angiogenesis.

T. Claim 12, which unlike the other method of use claims does not depend on claim 3, covers everything except cancer.

The traverse in these matters is unpersuasive, and much of it is very general. Applicants argue that their compounds block mitosis. Compounds which simply block mitosis --- e.g. microtubule inhibitors such as Vinblastine have been in use for some time, but none of them is even remotely effective against cancers generally. And the examiner notes that applicants have not established that their compounds are in fact microtubule inhibitors.

With regard to autoimmune disorders, applicants argue that "interfering with immune cell proliferation is one tool for ameliorating symptoms of autoimmune disease" and applicants name glucocorticoids as an example of compounds effective generally. This is confused. Ameliorating symptoms is not the same thing as treating the disorder itself. Pain is a symptom of bone cancer, but treating the pain is not a treatment of the cancer itself. The use of to glucocorticoids to deal with complications (such as serositis, vasculitis, or glomerulonephritis) of autoimmune disorders like SLE does not mean that it is treating the disorder itself. The examiner must also note that applicants have not established that their compounds act as glucocorticoids act.

With regard to apoptosis applicants correctly point out that "The point is that biologic processes are in balance." The claims, however, do not call for balance, but blocking apoptosis, period. The examiner must point further that one of the body's most powerful anti-cancer mechanisms is to increase apoptosis, not reduce it. For example, human papilloma viruses (HPV) can cause cervical cancer, which is named in claim 7. The

virus produces a protein (E6) that binds and thus inactivates the body's own apoptosis promoter p53, and thereby blocks the body's own apoptosis mechanism. If these compounds actually do suppress apoptosis (which has not been established), they would be expected to make the cervical cancer situation worse, not better.

(2) The nature of the invention and predictability in the art: The invention is directed toward medicine and is therefore physiological in nature. It is well established that "the scope of enablement varies inversely with the degree of unpredictability of the factors involved," and physiological activity is generally considered to be an unpredictable factor. See *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).

The traverse is unpersuasive. The fact that "physiology is a branch of science does" not mean that human find physiology unpredictable. For example, applicants on page 14 of their remarks mention angiogenesis. The prior art teaches that the regulation of angiogenesis is extraordinarily complex in the body. Numerous anti-angiogenesis factors have been identified in the body. Some of these are proteolytic fragments, such as angiostatin, Endostatin, Canstatin, Serpin antithrombin, PEX, Prolactin, Restin, Tumstatin, Arresten, Vasostatin, Kringle1-5, and Fibronectin fragments. There are also assorted cytokines and chemokines. These include IL-1 IL-4, IL-6, IL-10, IL-12 and IL–18, interferon-I, -9, and -K, EMAP-II, gro-9, IP-10, PF4, MIG and Platelet factor 4. There are also soluble receptors FGFR-1 and VEGFR-1 and the collagenase inhibitors TIMP-1, -2, -3, and –4. There are tumor suppressor genes p16 and p53. And there are all manner of others, including TGF-9, angiopoietin, angiotensin, SPARC, ChDI, angiotensin-2-receptor, caveolin, Retinoic acid, Troponin-1, Transforming growth factor 91, Thrombospondin-1, and -2, protamine, RGD sequence, Prostate specific antigen (PSA) Osteopontin cleavage

product, 2-methoxy estradiol, pigment epithelium derived factor, and others. In opposition to these are the endogenous pro-angiogenesis factors in the body. These include numerous growth factors, such as TGF-9, VEGF-A, -B, -C, -D, -E , VEGF-R2, placental growth factor, aFGF, hepatocyte growth factor, platelet-derived growth factors (of which there are four, PDGF-A, -B, -C, and –D, which can form homodimers and heterodimers, most importantly PDGF-BB), Platelet-derived endothelial cell growth factor (PD-ECGF), BFGF, HGF, IGF-1, EGF, Granulocyte colony-stimulating factor, and others. There are also cytokines and chemokines, including I-TNF IL-1, IL-6, IL-8, IL-13, IL-15, IL-18, transferrin, Basic Fibroblast Growth Factor (bFGF), ENA-78, Gro-alpha, CTAP-III, MCP-1, Fractalkine SDF-1 and others. There are cell Adhesion molecules, including Soluble E-selectrin, Soluble VCAM-1, Endoglin, CD31 (PECAM-1), CD34, MUC-18, sLx, Lewis-Y/H, alpha-v/beta-3 integrin and other beta-1 and beta-3 integrins, and others. There are also some enzymes, notably cathepsin, gelatinase A and B, and stromelysin. Others include copper ions, angiostatin-2, midkine, angiopoietin-1, nitric oxide synthase, CYR61 and CTGF, Angiotropin, prostaglandin E2, Angiogenin, Adrenomedullin, thrombopoietin, IGF-1, IGF-2, plasminogen activator inhibitor 1, thymidine phosphorylase, PAF, Prolactin, Substance P, pleiotropin, endothelin, human uterine angiogenesis factor (HUAF), erythropoeitin, urokinase tissue plasminogen activator, HBNF, Corpus luteum angiogenic factor (CLAF), B61, Type I collagen, Heparin, laminin, tenascin, Fibronectin, histamine, nicotinamide, adenosine, lactic acid, ACE, HAF and others. Even this listing, however, understates the complexity of this field. Thus, VEGF-A was listed as a growth factor. In fact, it has 6 isoforms, VEGF121, VEGF145, VEGF165, VEGF183, VEGF189 and VEGF206, produced by alternate splicing of the gene ("splice variants"). All six of these are expressed in varying

degrees by solid tumors, and there is in fact evidence that these might have differing biological functions. The extreme complexity of this entire system is seen by the fact that so far three factors, IL-1, IL-6 and TGF-9 have been identified as operating both pro-angiogenesis and anti-angiogenesis, depending on circumstances. Such complexity makes for a high level of unpredictability in the angiogenesis area. Similarly, applicants mention apoptosis, which is listed in certain claims. There are 3 independent mechanisms by which a cell commits suicide by apoptosis.

1.In the intrinsic (or mitochondrial) pathway, apoptosis is triggered by internal signals. The protein Bcl-2 , by a poorly understood mechanism, reacts to

Internal damage to the cell, and activates a related protein, Bax, which perforates in the outer mitochondrial membrane, causing cytochrome c to leak out.

The released cytochrome c binds to the protein Apaf-1 , which, using ATP,

aggregates to form apoptosomes. The apoptosomes bind to and activate caspase-9. Caspase-9 cleaves and thereby activates other caspases, notably caspase-3 and -7. These in turn =create an expanding cascade of proteolytic activity resulting in digestion of structural proteins in the cytoplasm, degradation of chromosomal DNA, and ultimately phagocytosis of the cell.

2. In the extrinsic or death receptor pathway, apoptosis is triggered by external signals: By an assortment of mechanisms, not all of which are understood, external sources, e.g. cytotoxic T cells trigger the production of the death activators FasL and a-TNF respectively. These transmits a signal to the cytoplasm that leads to activation of caspase 8, which then initiates a cascade of caspase activation leading to phagocytosis of the cell.

Example (right): When cytotoxic T cells recognize (bind to) their target,

3. A Third pathway does not involve capsases at all. When the cell receives a signal (the full nature of these signals not being fully understood), the protein AIF
is released from the intermembrane space of mitochondria and it migrates into the nucleus. There it binds to DNA, which triggers the destruction of the DNA and cell death. His pathway exists in neurons, but it is not clear what other cells it may also exist in.

The above is an extremely simplified picture; for example processes of signal amplification, exactly how and what capsase 8 activates, the role of p53 activating Bcl-2 and Bax, the roles of the PIG1-PIG13 genes in the process, and the function played by JNK activation are all complex maters. It appears that factors such as eIF4E, splicing factors such as SMN, FAIM, TLE1, AAC-11, fortilin (TPT1), prothymosin-alpha, eIF4E, gelsolin, and DFF tend to inhibit apoptosis, and factors such as the ALG family (e.g. ALG2, ALG3, STM-2), the NADE family (e.g. NADE, BEX, NGFRAP1), CIDE-3, Smac DIABLO, DAXX, CAD, IGFBP-3, STAG1, FLJ21908, TSAP6, HtrA2, PSAP, glycodelin A(PP14), SPARC, NRAGE, and IGFBP-3 promote, and there are still others whose role is unclear. There are in fact dozens and dozens of biological entities that have been identified as apoptosis factors, and many more are discovered each year. In most cases, little is known how these operate and are regulated, which makes the apoptosis system as a whole substantially unpredictable.

(3) Direction or Guidance: That provided is very limited. The dosage range information provided on page 44 is a range of 0.02-1 mg/kg/day, but this dosage range is of little value because it is completely generic. That is, it is the same dosage for all disorders listed in the specification, from asthma to cancer , which is a very substantial range of disorders.

In terms of specific disorders, there are vast pages of disorders listed, especially on pages 7-15 and 21-22. Applicants reply that "dosage determination is very routine". This is not true in certain areas, and cancer is certainly one of them. Many promising anti-cancer drugs have foundered because of an inability to find a dosage regimen that actually works.

(4) State of the Prior Art: The claimed compounds are piperidinyl-amino purines, with a particular substitution pattern at several positions. So far as the examiner is aware , piperidinyl-amino purines have not been successfully used as anticancer agents or for any other utility listed in the specification. .

(5) Working Examples: There are no working examples to the treatment of any actual disease. Table 2 shows inhibition of three CDKs, which cannot be said to be representative of the class as a whole (note that claim 23 is not rejected.) Table 3 lists test results in 3-5 cell lines, and example 4 gives results in xenografts on two cell lines, one an acute leukemia, and one for a prostate cancer. Applicants argue that the CDK are "expected to share similarities". They share some similarities in what they do in the body, but have some structural differences which means that typically drugs which inhibit some CDKs do not inhibit others. Although a number of CDK inhibitors have been studied, none of them are active generally against CDKs. Even the non-specific inhibitors flavopiridol and staurosporine are not active against e.g. CDK3 and CDK7 and others. This is mirrored in the fact that there are no proteins which generally activate them either. Indeed, none of the cyclins activate more than three of the CDKs. Thus, it appears that the CDKs are too dissimilar in structure for something to act on them generally.

(6) Skill of those in the art:

I. The prior art knows that there never has been a compound capable of treating cancer generally. There are compounds that treat a modest range of cancers, but no one has ever been able to figure out how to get a compound to be effective against cancer generally, or even a majority of cancers. Thus, the existence of such a "silver bullet" is contrary to our present understanding in oncology. Even the most broadly effective antitumor agents are only effective against a small fraction of the vast number of different cancers known. This is true in part because cancers arise from a wide variety of sources, such as viruses (e.g. EBV, HHV-8, and HTLV-1), exposure to chemicals such as tobacco tars, genetic disorders, ionizing radiation, and a wide variety of failures of the body's cell growth regulatory mechanisms. Different types of cancers affect different organs and have different methods of growth and harm to the body, and different vulnerabilities. Cancers that affect just a certain type of structure can be quite varied. Fibromas for example include Infantile myofibromatosis, Fibrous hamartoma of infancy. Juvenile hyaline fibromatoses. Infantile digital fibromatoses. Calcifying aponeurotic fibromas. Giant cell fibroblastoma. Ovarian fibroma, Dermatofibroma, myofibroma, myofibromatosis, desmoplastic fibroma, neurofibroma, peripheral odontogenic fibroma, peripheral ossifying fibroma, giant cell fibroma, Chondromyxoid Fibroma, Oral Neurofibroma, Juvenile aponeurotic fibroma (JAF), aggressive infantile fibromatosis (AIF), omental fibroma, Perifollicular fibroma, ameloblastic fibroma, Premalignant Fibroepithelial Tumor (Pinkus Tumor), Periungual fibroma (Koenen tumor), desmoid tumor, tracheal fibroma and many others. Even those that affect just a single organ are often not generally treatable. As an example, the main types of lung cancer are small cell (oat cell), giant cell, clear cell, adenocarcinoma of the lung, squamous cell cancer of the lung, and mesothelioma. There is no such thing as a

treatment of these generally because of their diversity. That is, there is no one compound that can treat these generally, or even most of them, nor is there any reason to think that there could be such a compound. Since it is beyond the skill of oncologists today to get an agent to be effective against cancers generally, evidence that the level of skill in this art is low relative to the difficulty of such a task. The skill thus depends on the particular cancer involved. There are cancers where the skill level is high and there are multiple successful chemotherapeutic treatments. In many, many cancers, however, there is no chemotherapy whatsoever available. As an example, one skilled in the art knows that chemotherapy of brain tumors is especially difficult. This is because 1) the blood-brain barrier, which is often intact in parts or all of a brain tumor, will block out many drugs, as it is the purpose of the blood-brain barrier to protect the brain from alien chemicals, and 2) CNS tumors are characterized by marked heterogeneity, which greatly decreases vulnerability to chemotherapy. As a result, many categories of CNS tumors simply have no chemotherapy available. These include, generally, hemangiomas and hemangioblastomas, low grade gliomas, meningiomas, craniopharyngiomas, acoustic neuromas, pituitary adenomas, optic nerve gliomas, glomus jugulare tumors and chordomas, to name just some. The majority of common cancers do not respond to chemotherapy.

The traverse on this point is unpersuasive. Applicants argue that some patients die during treatment, that less that cure is still beneficial and achievable, that dosages can be adjusted, etc., but this misses the point. Applicants are claiming treatment of all cancers. The prior art knows that there never has been a compound capable of treating cancer generally. "The cancer therapy art remains highly unpredictable, and no example exists for efficacy of a single product against tumors generally."

(<http://www.uspto.gov/web/offices/pac/dapp/1pecba.htm#7> ENABLEMENT DECISION TREE, Example F, situation 1) There are compounds that treat a modest range of cancers, but no one has ever been able to figure out how to get a compound to be effective against cancer generally, or even a majority of cancers. Thus, the existence of such a "silver bullet" is contrary to our present understanding in oncology. There are many CDK inhibitors, around, a few of which are anti-cancer agents, but none of them have been found effective for anything remotely resembly cnacer generally,, and applicants present no evidence that their compounds are the revolutionary exception.

II. There are both chronic and acute "autoimmune diseases", most of which lack satisfactory treatment. The intractability of these disorders is clear evidence that the skill level in this art is low relative to the difficulty of the task. Under such circumstances, it is proper for the PTO to require evidence that such an unprecedented feat has actually been accomplished. The failure of skilled scientists to achieve a goal is substantial evidence that achieving such a goal is beyond the skill of practitioners in that art, *Genentech vs. Novo Nordisk*, 42 USPQ2nd 1001, 1006.

Since no compound has shown clinical efficacy against all autoimmune diseases, thus no *in vivo* or *in vitro* assay could be validated for the identification of such a general agent. Applicants' specification logically must lack such assay data.

In fact, there are four basic mechanisms underlying autoimmune disease: 1. Antibody mediated diseases: a specific antibody exists targeted against a particular antigen (protein), which leads to its destruction and signs of the disease. Examples are: auto-immune mediated hemolytic anemia, where the target is on the surface of the red blood cell; myasthenia gravis where the target is the acetylcholine receptor in the neuromuscular

junction; hypoadrenocorticism (Addison's) where the targets are the cells of the adrenal gland. 2. Immune-complex-mediated diseases: antibodies are produced against proteins in the body. These combine into large molecules that circulate around the body. In systemic lupus erythematosus (SLE) antibodies are formed against several components in the cell's nucleus (hence the anti-nuclear antibody test (ANA) for SLE). Most notably antibodies are made against the body's double stranded DNA, and form circulating soluble complexes of DNA and antibody, which break down in skin causing an increased sensitivity to ultraviolet light and a variety of signs. As the blood is filtered through the kidneys, the complexes are trapped in the glomeruli and blood vessels, causing the kidney to leak protein - glomerulonephritis. They also cause leakage in other blood vessels, and there may be hemorrhaging, as well as accumulating in synovial fluid and causing signs of arthritis and joint pain. Rheumatoid arthritis results from immune complexes (IgM class antibody called rheumatoid factor) against part of the patient's own immune system (part of its IgG molecules). These form complexes that are deposited in the synovia of the joint spaces causing an inflammatory response, joint swelling, and pain. The collagen and cartilage of the joint breaks down and is eventually replaced by fibrin which fuses the joints - ankylosis. 3. Antibody and T Cell-mediated diseases: T cells are one of two types (the other being B-cells), which mediate immune reactions. Upon exposure to a particular antigen, they become programmed to search for and destroy that particular protein in future. Once a patient has been exposed to an antigen, he will be able to mount a much faster response to it the next time it encounters it. This is the basis of vaccination. Thyroiditis (autoimmune hypothyroidism) seems to be of mixed etiology. Several target antigens have been identified, including thyroglobulin the major hormone made by the thyroid. Auto-antibodies

to antigens in the epithelial cells of the thyroid have also been found. The thyroid becomes invaded by large numbers of T and B cells as well as macrophages, which are cells that engulf and destroy other cell types. T cells specifically programmed for thyroglobulin have been identified. Autoimmune disorders can arise from the killer T-cells, from the helper T-cells, or from the regulatory T-cells (e.g. IPEX syndrome). 4. Diseases arising from a deficiency in complement: When an antigen and antibody react they may activate a series of serum enzymes (the complement system) whose end result is either the lysis (breakup) of the antigen molecule or to make it easier for phagocytic cells like the macrophages to destroy it. Patients with deficiencies in enzymes activated early in the complement system develop autoimmune diseases like SLE. Thus, with such greatly differing mechanisms, it is not logical that a treatment for autoimmune diseases generally can be found.

Applicants response here is not entirely understood. Applicants refer to one type as "non-working embodiments." If these are non-working, why are they being claimed? In another place, applicants sate that "Preventing or minimizing activation and proliferation of B cells...", but applicants have not shown that their compounds do, in fact, prevent the activation, etc of B-cells. In fact, the examiner cannot even locate, in this 183 page specification, even any mention of applicants compounds having any effect at all on B-cells.

III. Claim 14 lists some autoimmune disorders, Type 1 diabetes, atherosclerosis and asthma. Such disorders have never been treated successfully with agents that suppress the immune system, and of course there is no evidence at all that these compounds do in fact suppress the immune system. Moreover, atherosclerosis itself is not per se treatable.

Applicants response focuses on p21, which applicants assert "is known to be involved in immune system functioning" etc. Again, the examiner cannot find any mention in the specification of p21being affected by these compounds.

IV. One of ordinary skill in the art knows that one of the methods of promoting tumor regression is by inducing apoptosis. These compounds, alleged to be anti-cancer agents, are said to prevent apoptosis. Similarly, autoimmune disorders such as lupus or MS are characterized by too little apoptosis, and so agents which suppress apoptosis would be expected to make matters worse.

V. While sarcomas are listed, sarcomas generally speaking do not respond particularly well to primary chemotherapy, especially as compared to many other types of tumors. Instead, sarcomas are more frequently treated with surgery, or radiation, or even regional hyperthermia (RHT), and Photodynamic therapy (PDT).

Applicants respond that "surgery is often used in conjunction with other modes of treatment, including chemotherapeutic agents." This is certainly true for areas such as carcinomas of the bladder, breast, lung, etc. But this is generally not true for sarcomas, since these are often treated either with surgery alone, or with surgery plus something other than chemotherapy, e.g. radiation. Examples would be retroperitoneal SUBSTITUENTS and pediatric chondrosarcomas.

VI. With regard to claim 22, although a number of CDK inhibitors have been studied, none of them are active generally against CDKs. Even the non-specific inhibitors flavopiridol and staurosporine are not active against e.g. CDK3 and CDK7 and others. This is mirrored in the fact that there are no proteins which generally activate them either. Indeed, none of

the cyclins activate more than three of the CDKs. Thus, it appears that the CDKs are too dissimilar in structure for something to act on them generally.

Moreover, many of the CDKs have an unknown connection to disease. For example CDK8 when associated with cyclin C phosphorylates CTD RNA pol II, but on different site than where CDK7 operates. However, that is not enough to connect the CDK (or CDK7 for that mater) to the treatment of any disease. There are no known inhibitors for these, either natural proteins or synthetic small molecules. CDK3 is even more poorly understood; it isn't even known what substrates (if any) it operates on.

(7) The quantity of experimentation needed: Given the fact that historically the development of new cancers drugs has been difficult and time consuming, and especially in view of factors 1, 6 and 4, the quantity of experimentation needed is expected to be great.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1, and 24-35 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-10 of U.S. Patent No. 6861524. Although the conflicting claims are not identical, they are not patentably

distinct from each other because the claims here are just generic to the species already patented in the parent case.

Information Disclosure Statement

The information disclosure statement filed 3/2/06 fails to comply with 37 CFR 1.98(a)(2), which requires a legible copy of each cited foreign patent document; each non-patent literature publication or that portion which caused it to be listed; and all other information or that portion which caused it to be listed. The one missing document was struck from the PTO-1449.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, THIS ACTION IS MADE FINAL. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Mark L. Berch whose telephone number is 571-272-0663. The examiner can normally be reached on M-F 7:15 - 3:45.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James O. Wilson can be reached on (571)272-0661. The fax phone numbers for the organization where this application or proceeding is assigned are (571) 273-8300 for regular communications and (571) 273-8300 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0198.

Mark L. Berch
Primary Examiner
Art Unit 1624

March 22, 2006